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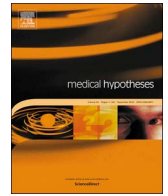
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How extreme dieting becomes compulsive: A novel hypothesis for the role of anxiety in the development and maintenance of anorexia nervosa



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ABSTRACT

The US National Institute of Mental Health's Research Domain Criteria (NIMH RDoC) advocates the study of features common to psychiatric conditions. This transdiagnostic approach has recently been adopted into the study of anorexia nervosa (AN), an illness that can be considered compulsive in nature. This has led to the development of an account of AN that identifies key roles for the heightened reinforcement of starvation, leading to its excessive repetition, and goal-directed system dysfunction. Considering models of illness in other compulsive disorders, we extend the existing account to explain the emergence of reinforcement and goal-directed system abnormalities in AN, proposing that anxiety is central to both processes. As such we emphasise the particular importance of the anxiolytic effects of starvation, over other reinforcing outcomes, in encouraging the continuation of starvation within a model that proposes a number of mechanisms by which anxiety operates in the development and maintenance of AN. We suggest the psychopathology of AN mediates the relationship between the anxiolytic effects of starvation and excessive repetition of starvation, and that compulsive starvation has reciprocal effects on its determinants. We thus account for the emergence of symptoms of AN other than compulsive starvation, and for the relationship between different features of the disorder. By extending and adapting an existing explanation of AN, we provide a richer aetiological model that invites new research questions and could inform novel approaches to prevention and treatment.

Introduction

Anorexia nervosa (AN) is a mental illness whereby a dangerously low body weight is maintained by extreme dietary restriction [1]. The abnormal eating behaviour that is central to AN [2] persists despite its adverse effects on daily and social functioning [3], and physical health [4]. AN affects approximately 1–2% of Western populations, and has the highest mortality rate of any psychiatric illness, this figure approaching 6.0% [5].

AN tends to be chronic, with less than 50% of individuals who develop the illness making a full recovery [6,7]. It is suggested that current pharmacological and psychological therapies cannot address the neurobiological factors or mechanisms responsible for illness development and maintenance because it is unclear what these are [8]. To better understand the aetiology of psychiatric illnesses, Research Domain Criteria (RDoC), resulting from the National Institute of Mental Health (NIMH) 2008 strategic plan [9], encourages a transdiagnostic approach [10,11]. Central to this approach is investigating the causes of

features common to a number of disorders, rather than the causes of symptoms specific to discrete diagnostic categories [12]. Studying the characteristics that AN shares with other psychiatric disorders can allow new and testable theories of AN aetiology to be developed [13]. Potentially causal neural abnormalities that have not previously been considered in aetiological models of AN can be highlighted using this transdiagnostic approach [14].

Compulsivity has been identified as a transdiagnostic trait that is central to obsessive-compulsive disorders and substance and behavioural addictions. Compulsivity describes a tendency to engage in repetitive and stereotyped acts that have unwanted outcomes [15], and arises from a reduced ability to control inflexible yet maladaptive behaviour [16]. Recently compulsive behaviour has been characterised as an imbalance between the influence of the goal-directed system (the ventral medial prefrontal cortex; vmPFC) and the habit system (the dorsal striatum; [17,18]). The habit system guides behaviour based on past outcomes of actions, due to the formation of stimulus-response (S-R) links, a process that occurs when a response produces a favourable

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outcome. S-R links strengthen with behavioural repetition and their establishment allows stimuli to initiate the responses they are paired with automatically, even when these responses are inappropriate [19]. In contrast, the goal-directed system considers predicted outcomes of various actions, and the present value of these outcomes, to elicit behaviour tailored to the current situation [20]. It is suggested that compulsive behaviour arises from a failure of the goal-directed system to override the influence of the habit system when the latter produces maladaptive responses [21].

Steinglass and Walsh [22] and Walsh [2] proposed that the extreme restriction of food intake that epitomises AN is habitual. Later Park and colleagues proposed this behaviour to be compulsive [13,23]. Indeed starvation persists in the face of negative consequences, both immediate, for example interfering with academic/occupational/social interests, and longer-term; the behaviours promoting further, and potentially dangerous, weight-loss. Although individuals with AN often express desires to recover [22], they are seemingly unable to stop engaging in behaviour that contributes to the maintenance of an extremely low weight [24,25].

Godier and Park [13] considered models of compulsivity developed in relation to other disorders to propose the importance of both the reinforcement of starvation, and of a goal-directed system deficit, in the development of compulsive starvation. Greater reinforcement of starvation is suggested to cause excessive repetition of behaviour conducive to caloric restriction. Combined with a reliance on the habit-system for learning and behavioural control, this excessive repetition results in the development of strong S-R habits surrounding dietary restriction that are able to exert a dominant influence over behaviour.

In this paper we consider factors and mechanisms identified as relevant to reinforcement and goal-directed system abnormalities in other compulsive disorders to understand how these develop in AN. Thus we adopt a transdiagnostic approach to extend the aetiological model of AN proposed by Godier and Park [13]. We also adapt the existing account to highlight the particular importance of the anxiolytic properties of dietary restriction, over other potentially reinforcing effects of the behaviour, and explain the emergence of symptoms of AN other than compulsive starvation.

A novel model of anorexia nervosa development and maintenance

In brief, we suggest high levels of anxiety serve to make the anxiolytic effects of dietary restriction more reinforcing, and that anxiety contributes to reduced function of the goal-directed system. Thus, we propose a central role for anxiety in the development of compulsive starvation, with part of the novelty of our hypothesis being in the dual mechanisms by which anxiety is suggested to operate in AN onset. We propose that the reinforcing effects of starvation cause excessive repetition of behaviour via the development of psychological symptoms of AN. We also suggest that starvation becoming compulsive has adverse implications on anxiety, the goal-directed system, and psychological symptoms of AN, to encourage the formation of a vicious cycle that ensures the persistence of extreme dietary restriction. The proposed aetiological model is displayed in Fig. 1 below.

Given the complexity of AN we fully recognise the involvement of factors additional to those included in the proposed model, however we suggest testing the set of central hypotheses proposed here prior to expanding the model further. In the following section we outline each part of the model, and provide evidence to support inclusion of the factor or pathway.

1. Individuals who develop AN experience high levels of anxiety

Clinical observations characterize individuals with AN as highly anxious, and this is supported by empirical studies reporting greater trait anxiety and higher rates of anxiety disorders in AN populations as compared to the general population [26]. Importantly anxious

pathology is consistently documented to precede AN onset [27–30], supporting a role of anxiety in AN development. Notably high levels of anxiety tend to also precede the onset of addiction and OCD [31,32].

2. Dietary restriction is anxiolytic, and the relief of anxiety (or negative reinforcement) provided by dietary restriction increases with anxiety

Engagement in dietary restriction reduces activity of serotonin (5-HT) and noradrenalin (NA) systems that modulate anxiety, due to reduced intake of the dietary precursors of the neurotransmitters (tryptophan for 5-HT, and tyrosine for NA; [33,34]). Indeed, ill AN women have reduced 5-HT metabolites in their cerebral spinal fluid, reduced concentrations of NA in their blood plasma, and excrete reduced NA metabolites, compared to healthy women [35,36]. Recovered AN women have elevated levels of 5-HT metabolites [36], and gene variants linked to more active 5-HT and NA systems are implicated in AN [34,37], supporting the involvement of these neurotransmitter systems in the heightened anxiety that precedes AN. Increased ratios of omega-3:omega-6 fatty acids are suggested to result from a calorie and fat restricted diet, and there is some evidence that this ratio is negatively related to anxiety in AN [38], providing another mechanism by which dietary restriction could ameliorate anxiety.

Anxiety relief is easier to achieve, and more beneficial, for anxious individuals, such as those who develop AN, suggesting starvation has greater anxiolytic effects in these individuals [39,40]. Experimentally induced tryptophan depletion significantly reduced anxiety in women receiving inpatient treatment for AN, and those recovered from the illness, but did not affect the anxiety levels of healthy women [33]. These results can be explained by floor effects given the baseline anxiety of healthy women was comparable to that of current/recovered AN women following tryptophan depletion.

3. Experiencing greater anxiolytic effects of dietary restriction gives rise to the psychological symptoms of AN

The effects of greater reinforcement of starvation (which we propose to consist of anxiety relief) are proposed by O'Hara et al. [41] to result in the induction of a strong drive to starve. The drive to starve in turn results in fears of stimuli/behaviours not conducive to restrictive eating, such as food and weight-gain, and preoccupations with eating and weight [41]. These drives, fears and preoccupations collectively represent AN psychopathology [42].

4. AN psychopathology causes excessive repetition of behaviour that is conducive to starvation

Like O'Hara et al. [41] we suggest AN psychopathology directly encourages the excessive repetition of dietary restriction that results in habit formation. Interestingly individuals with AN may be physiologically more able to engage in starvation over the period of time required for habits surrounding the behaviour to form given enhanced 5-HT activity increases satiety as well as anxiety [43]. The intestinal microbiota of individuals with AN may possess unique characteristics that also contribute to the ability to maintain a diet that is severely calorie restricted [44].

Given the alleviation of anxiety is proposed to promote AN psychopathology we suggest heightened anxiolytic effects of dietary restriction, resulting from greater baseline anxiety, encourages continuation of the dietary restriction, albeit indirectly. Similarly, avoiding an aversive state, and particularly an anxious one, is proposed to motivate continued drug-taking, hair-pulling, gambling and behaviours that become compulsive in OCD [45–48].

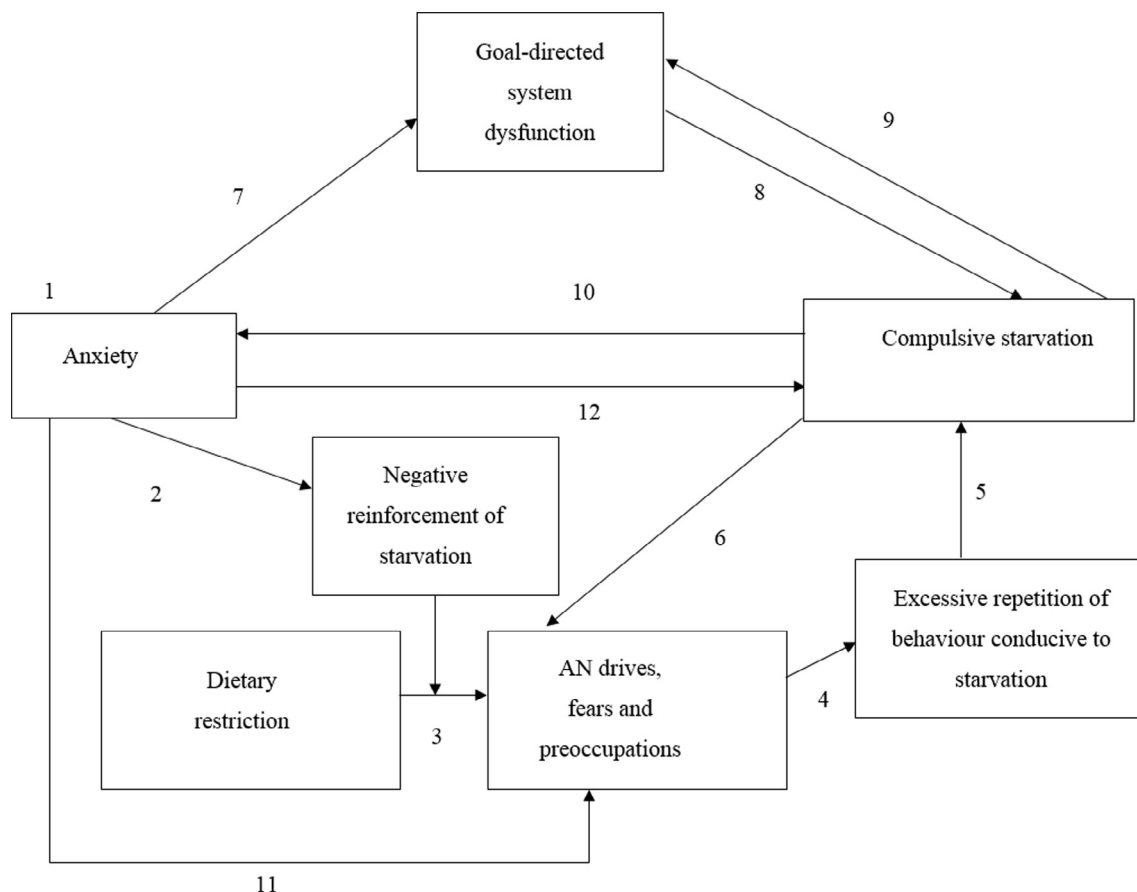


Fig. 1. The hypothesised model of anorexia nervosa development and maintenance.

5. Excessive engagement in dietary restriction contributes to the development of compulsive starvation

The dominance of behavioural habits increases with their repetition [19]. Thus, like with other compulsive disorders, one pathway by which the maladaptive behaviour of AN (starvation) becomes resistant to the influence of the goal-directed system is via excessive engagement in the behaviour [13,49].

6. The compulsive nature of starvation intensifies AN psychopathology

Compulsive behaviour has an urge-like characteristic [49], thought to result from the habit system exerting a dominant influence [21], and certainly individuals with AN report a “need” to engage in starvation [24]. Thus starvation becoming compulsive may increase the drive to starve, which then heightens fears of food and weight-gain, and preoccupations with eating and weight. Relationships of compulsive starvation, and rituals/compulsions surrounding eating, with the psychopathology of AN have been reported [25,50,51]. This further explains how the emergence of compulsivity in AN is detrimental to recovery, given disorder drives, fears and preoccupations are associated with a lack of motivation to eat and gain weight [52].

7. Anxiety causes goal-directed system dysfunction in AN

Goal-directed system dysfunction in OCD and addiction is suggested to derive from anxiety [18,53]. This is because anxiety gives rise to stress [54], and stress promotes the use of the habit system over the goal-directed system, and is associated with increased volume and activity of the dorsal striatum [55]. These effects are thought to be due to goal-directed system dysfunction since enhanced activity of

glucocorticoid and noradrenergic systems, that serves to impair pre-frontal cortex (PFC) function, also co-occurs with stress [54,56]. Further supporting anxiety causing goal-directed system dysfunction, under conditions of anxiety attention is governed by the stimulus-driven system, and not the goal-directed system [57].

Evidence for goal-directed system dysfunction in individuals with AN comes from studies reporting altered vmPFC volume in individuals with AN compared to healthy women [58,59]. The vmPFC is hyper-active in response to pictures of food in AN [60,61], and individuals with the disorder consistently show deficits on set-shifting tasks that depend on vmPFC integrity [13]. In a non-clinical population Gillan et al. [62] found the severity of desires to be thin, and preoccupations with weight, that are typical of AN, increased with decreased recruitment of the goal-directed system to complete a task, which is suggested to reflect poor function of this system. Godier et al. [63] found individuals with AN learnt relationships between actions and outcomes in a similar manner to healthy women, suggesting comparable goal-directed system function of the two groups. It may be that inefficiencies of the goal-directed system could not be detected behaviourally with the particular task however. Further, a reliance on the habit system in AN individuals is indicated by their heightened dorsal striatal activity, relative to healthy women, during reward learning tasks [64,65], and when making decisions about what to eat [66].

8. Goal-directed system impairment contributes to the development of compulsive starvation

For individuals with OCD and addictive disorders goal-directed system abnormalities correlate with the development and control of behavioural habits generally, not just those relevant to the specific disorder [67,68]. Similarly, we propose that in AN goal-directed system

dysfunction impacts behaviour globally, but specifically promotes the development of compulsive starvation when dietary restriction is repeatedly engaged in. Thus we suggest anxiety encourages the development of compulsive starvation via two pathways: 1. by causing goal-directed system dysfunction; and 2. by heightening the reinforcement of starvation to cause its excessive repetition.

9. Continued starvation, resulting from the dietary restriction now being compulsive, weakens the goal-directed system further

Starvation increases the production of stress hormones that impair the goal-directed system [26]. In addition, the depletion of tryptophan or tyrosine, both of which are outcomes of starvation [33,34,65], causes a reliance on the habit system for learning [69,70], suggested to result from reduced function of the goal-directed system [71]. Further impairment of the goal-directed system means withholding the restrictive eating habits that have developed becomes less possible.

10. The compulsive nature of starvation maintains high levels of anxiety

Key to compulsivity is the extremely aversive state that is experienced when compulsions are not performed, which results from adaptations within neurobiological systems that mediate reward and affect, following repeated performance of the particular behaviour [13]. This is well characterised in addiction and OCD, where compulsions are performed to temporarily alleviate negative affect [72–74]. Individuals with AN experience very high levels of anxiety when they do eat, or when starvation is not engaged in, and this anxiety becomes food and weight focused [13]. The resurgence of anxiety, to levels even greater than previously (before food restriction was engaged in), is suggested to be partly mediated by enhanced sensitivity of 5-HT and NA systems, which have adapted in response to reduced intake of tryptophan and tyrosine respectively [75,76].

11. Heightened anxiety aggravates AN psychopathology

When starvation becomes necessary to avoid an extremely anxious state the desire to starve is enhanced. This is particularly so given the poor emotion regulation abilities of individuals with AN limits the use of alternative strategies to overcome dysphoria [93], and increases in the desire to starve results in increases in the fears and preoccupations of AN. Indeed studies have reported relationships between anxiety and AN psychopathology in clinical populations [77,78].

12. Anxiety becomes able to trigger restrictive eating

Anxiety precedes and coincides with restrictive eating in AN [79–81], which is not the case for individuals without the disorder [82]. Repeatedly engaging in dietary restriction in an anxious state conceivably enables anxiety to become able to directly evoke restrictive eating habits, due to a pairing of emotion and behaviour, or the formation of a S-R link. Increased state anxiety is related to reduced inhibitory control in individuals with AN [83], and we propose anxiety impairs the goal-directed system. Thus a number of mechanisms likely explain how anxiety promotes engagement in maladaptive dietary restriction habits that have developed in the course of a compulsive illness.

Summary

Our model proposes that the anxiety of individuals with AN predisposes them to the development of, and reliance on, habits by affecting the function of the goal-directed system, and encouraging the repetition of anxiolytic behaviours. While such promotes compulsivity generally, when dieting behaviour is engaged for a sufficient period, which is possible in AN due to unique biological factors, the

compulsions surround dietary restriction. The formation of such compulsions has a negative impact on the determinants of compulsive starvation, promoting the maintenance of AN pathology. Thus we suggest a number of factors and mechanisms act synergistically in the development and persistence of a complex illness.

Comparison with other theories

We have repositioned anxiety in the model of Godier and Park [13] and proposed novel mechanisms by which anxiety acts in AN to explain the emergence of reinforcement and goal-directed system abnormalities in the disorder. Park and colleagues propose starvation continues initially in individuals with AN because weight loss is highly rewarding, the rewarding effects being positive comments from others about one's body and a sense of achievement [13,23]. Only with progression of AN is the avoidance of negative emotions, or negative reinforcement, suggested to be relevant to on-going starvation. In contrast we focus on the anxiolytic properties of dietary restriction as the initial motivation for continued engagement in the behaviour. We recognise that dietary restriction has positively reinforcing effects, however whether these effects are greater for individuals who develop AN, is unknown. Conversely anxiolytic effects of behaviour are increased when anxiety, a known risk factor for AN, is greater.

Also in contrast to Godier and Park's [13] model we suggest that experiencing greater reinforcement (and specifically anxiety relief) from starvation encourages further starvation via the development of the psychological symptoms of AN, as was proposed by O'Hara et al. [41]. In this way we are able to account for the emergence of these psychological symptoms, as well as behavioural features of the disorder, and relationships between the two. Finally, our model further extends that of Godier and Park [13] by outlining the implications that starvation being compulsive has on other disorder-relevant factors. This is important since it means we are better able to account for the persistence of AN.

Kaye and colleagues [8,33] and Nunn et al. [34] have previously proposed that the anxiolytic properties of dietary restriction explain why anxious individuals are more likely to repeatedly and excessively engage in the behaviour, and thus why heightened anxiety is a risk factor for AN development and maintenance. These accounts propose either 5-HT [8,33] or NA systems [34] underlie high levels of anxiety, and mediate the anxiolytic effects of starvation, in AN. In contrast we suggest the involvement of both neurotransmitter systems, and acknowledge mechanisms other than changes to tryptophan and tyrosine intake by which a calorie and fat restricted diet may reduce anxiety. Our account also differs in that we suggest anxiety operates in the development and maintenance of AN through effects on goal-directed and inhibitory control systems, in addition to affecting the reinforcement (or heightening the anxiolytic properties) of starvation. In addition, the proposal that anxiety becomes able to cue food avoidance through S-R mechanisms is unique to our hypothesis.

Implications for treatment and prevention

Treatment

The treatment implications of starvation being habitual or compulsive in AN have been discussed by Godier and Park [13] and will not be considered here. We will instead focus on the implications of the proposal that anxiety has a key role in the maintenance of AN. This proposal suggests a need for AN interventions to focus on alleviating anxiety and training individuals to manage the emotion, which is not a priority of the treatments that are currently used widely.

Improved emotion regulation can be achieved with psychological therapies that teach individuals effective and safe methods to manage and express their feelings, such as Emotion Acceptance Behaviour Therapy [84], which has been trialled in the treatment of AN. Ideally

extremely anxious states are avoided, but when such states do arise individuals should be better able to employ successful anxiolytic techniques that do not involve starvation, as a result of the therapy. A recent pilot of EABT in adolescents found it had clinically significant effects on AN symptoms, which were maintained at the 6 month follow-up point [85].

We suggest anxiety becomes able to cue food avoidance, making re-feeding particularly difficult given the anxiety evoked by food and eating in AN. As such we recommend treatments that seek to reduce anxiety around eating, such as Exposure and Response Prevention therapy for AN (AN-EXRP; [86]), which also aims to encourage the effortful withholding of automatic restrictive eating responses. In AN-EXRP patients are presented with food items and supported in consuming these without concurrently/subsequently resorting to endorsed rituals or routines that promote dietary restriction [87]. The repeated exposure to, and consumption of, feared foods in AN-EXRP reduces anxiety by way of habituation, while also lessening the influence of maladaptive food avoidance habits [86,88].

Pharmacological interventions seeking to normalise neurotransmission within 5-HT and NA systems may be of great value in the treatment of AN given evidence for the involvement of these systems in the anxiety of AN. Development of such an intervention is in progress, with Hart et al. [75] releasing a rationale, and plan, for a trial of tyrosine supplementation treatment for AN. Findings from experimental trials of such pharmacological interventions can elucidate the role of neurotransmitter systems in AN to enable a better understanding of the disorder. Attempts to identify effective pharmacological treatments for AN are encouraged given the potential to reduce costs of treatment and enhance its accessibility.

Future research might explore the efficacy of anxiolytic interventions that have shown success in other disorders in the treatment of AN. This would allow for a transdiagnostic approach to the treatment, as well as the study, of AN, potentially resulting in vastly improved outcomes. Investigating the mechanisms by which existing and novel anxiety-targeted treatments operate to improve eating behaviour, for example by affecting goal-directed system function or AN psychopathology, will also inform the validity of our model.

Prevention

Highlighting anxiety as a key risk factor for AN allows the identification of individuals for whom existing prevention interventions could be most beneficial, enabling improved efficacy. As the influence of heightened reinforcement of starvation and goal-directed system dysfunction, proposed to mediate the effects of anxiety on AN development, are dependent on initiation of dieting behaviour, further justification for the targeting of this dieting behaviour by existing prevention interventions is provided by our model. The Body Project [89] and Healthy Living intervention [90] successfully reduce the practicing of unhealthy/extreme weight control methods in adolescents/young adults. This is thought to be responsible for the significantly lower number of AN cases that subsequently develop in intervention, as compared to control, groups [91].

Risk factors of the model may be targets for prevention, as well as treatment, interventions. Training for adolescents that improves their emotion regulation ability, and goal-directed system function, to reduce anxiety, and lower vulnerability to forming habits, respectively, may be valuable additions to existing eating disorder prevention programmes. Mindfulness interventions might be particularly useful given these improve emotion regulation [92], and reduce dietary restraint [93]. Initial studies indicate the utility of mindfulness-based techniques in AN prevention, but the trialled interventions require refinement for their efficacy to be maximised [93].

Conclusion

Having formulated AN as a compulsive disorder and taking a transdiagnostic approach to studying the illness, theorists have proposed the reinforcement of starvation, and goal-directed system dysfunction, as causal in the onset of AN. By extending and adapting this account of AN we have been able to highlight the particular relevance of anxiety to the aetiology of the disorder, as well as account for the emergence of psychological symptoms of AN in addition to compulsive starvation. The hypotheses proposed should be tested to allow the validation and improvement of the model, which may then be expanded to include other explanatory factors. The model can justify the use of existing and planned prevention and treatment programmes, but may also guide the development of novel interventions to favourably affect the incidence and recovery rates of a life-threatening condition.

Conflict of interest statement

None of the authors have any conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.mehy.2017.09.001>.

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